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Therapeutic Class Review
Cyclooxygenase-2 (COX-2) Inhibitors

Overview/Summary

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of medications. The primary effect of the NSAIDs is to inhibit cyclooxygenase (COX), thereby impairing the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The extent of enzyme inhibition varies among the different NSAIDs, although there are no studies relating the degree of COX inhibition with anti-inflammatory efficacy in individual patients.[1]

Two related isoforms of the COX enzyme have been identified: COX-1 and COX-2. COX-1 is expressed in most tissues. It regulates normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function), and is stimulated by hormones or growth factors. COX-2 is expressed in the brain, kidney, and bone. Its expression at other sites is increased during states of inflammation.[2,3] Thus, differences in the extent with which a particular NSAID inhibits an isoform of COX affects both its activity and toxicity.

NSAIDs have been used to treat various conditions, including rheumatoid arthritis, osteoarthritis, and pain. Long-term NSAID therapy is associated with significant gastrointestinal irritation and the potential for the development of life-threatening gastrointestinal ulcers. Epidemiologic studies have demonstrated that the prevalence of significant gastrointestinal complications has been estimated to be 1% to 4% annually with chronic use of NSAIDs.[4] In the United States, complications secondary to their use result in an estimated 10,000 to 20,000 deaths and 200,000 to 400,000 hospitalizations each year.[5,6] These toxicities significantly limit the therapeutic potential of this class of medications. An NSAID that inhibits the inducible COX-2 isoform (thereby decreasing inflammation) without having any effect on the COX-1 isoform (thereby minimizing toxicity) would maximize effectiveness, without inducing toxicity.

COX-2 inhibitors are a newer class of NSAIDs developed to reduce the gastric complications associated with traditional NSAIDs. Celecoxib (Celebrex®) is approved by the Food and Drug Administration (FDA) for the treatment of ankylosing spondylitis, osteoarthritis, rheumatoid and juvenile rheumatoid arthritis, the management of acute pain, the treatment of primary dysmenorrhea, and as an oral adjunct to the usual care for patients with familial adenomatous polyposis.[7-8]

In 2004, Merck & Co., Inc. announced a voluntary withdrawal of their product rofecoxib (Vioxx®) from the United States and the worldwide market due to safety concerns of an increased risk of cardiovascular events in patients. In 2005, the FDA asked Pfizer to voluntarily remove valdecoxib (Bextra®) from the market. The FDA has issued supplemental request letters to sponsors of all NSAIDs requesting that they make labeling changes to their products. These letters include recommended proposed labeling for both the prescription and over-the-counter NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including celecoxib have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular events and the serious, potential life-threatening gastrointestinal bleeding associated with their use.[9]

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Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Celecoxib (Celebrex®)	Cyclooxygenase-2 (COX-2) inhibitors	-

Indications

Table 2. Food and Drug Administration Approved Indications[7-8]

Indication	Celecoxib
Ankylosing spondylitis	✔
Familial adenomatous polyposis	✔
Juvenile rheumatoid arthritis	✔
Osteoarthritis	✔
Pain, acute	✔
Primary dysmenorrheal	✔
Rheumatoid arthritis	✔

Potential off-label uses for celecoxib include prophylaxis and adjunct treatment for patients with coronary stent stenosis, treatment of chronic paroxysmal hemicrania, and the treatment of systemic lupus erythematosus.[8]

Pharmacokinetics

Table 3. Pharmacokinetics[7]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Celecoxib	Due to low solubility, absolute bioavailability studies have not been conducted	CYP2CP	Renal (27); feces (57); unchanged (<3)	Not specified	11.2

Clinical Trials

Clinical trials comparing celecoxib with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) for the relief of signs and symptoms associated with osteoarthritis have been published and are summarized in table 4. In addition, a trial comparing the efficacy of rofecoxib, celecoxib, and acetaminophen (APAP) in treating osteoarthritis of the knee is also summarized in table 4.[10] This trial compares the 3 agents, and results indicate that 25 mg/day of rofecoxib provided statistically significant advantages over celecoxib and APAP for many measures of symptomatic osteoarthritis of the knee. In general, cyclooxygenase-2 (COX-2) inhibitors have efficacy comparable to that of conventional NSAID therapy including piroxicam, naproxen, diclofenac, ibuprofen, and nabumetone. The differences between the agents are mainly in their reported tolerability profiles; with COX-2 inhibitors generally better tolerated than conventional NSAIDs. This better tolerability profile is particularly noted with regard to gastrointestinal adverse events.

Trials evaluating the use of COX-2 inhibitors in rheumatoid arthritis have been performed with celecoxib. Results of 2 studies comparing celecoxib with diclofenac[11] and naproxen[12] demonstrated similar efficacy. The only significant difference reported was in favor of 200 mg of celecoxib administered orally twice daily when compared to 500 mg of naproxen administered orally twice daily as measured by patient's and physician's global assessments.[12] This difference, however, was not found between a 400-mg dose of celecoxib and a 500-mg dose of naproxen both administered orally twice daily.

Many of the studies that evaluate the use of the COX-2 inhibitors for the treatment of pain are as either a loading dose or a single dose post-intervention. In a study by Reuban et al, celecoxib and rofecoxib were observed to have similar analgesic effects in the initial 4-hour postsurgical period in patients undergoing

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elective decompressive lumbar laminectomy. Rofecoxib, however, was associated with a significantly greater duration of analgesic activity.[13] In another comparative trial, patients who had undergone dental surgery received a single dose of celecoxib, rofecoxib, naproxen, or placebo postoperatively.[14] Again, the analgesic activity of rofecoxib was found to be superior to that of celecoxib.

Clinical trials have been published evaluating the efficacy of celecoxib for the prevention of colorectal cancer in patients with familial adenomatous polyposis (FAP).[15,16] A randomized, double-blind, placebo-controlled study was conducted in patients with FAP.[15] The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype. One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for celecoxib 400 mg twice daily, 12% for celecoxib 100 mg twice daily and 5% for placebo. The reduction in polyps observed with celecoxib 400 mg twice daily was statistically superior to placebo at six months (P=0.003).

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Osteoarthritis				
Bensen et al[17] Celecoxib 50 mg PO BID vs celecoxib 100 mg PO BID vs celecoxib 200 mg PO BID vs naproxen 500 mg PO BID vs placebo	DB, MC, PC, PG, R Patients with symptomatic OA of the knee	N=1,003 12 weeks	Primary: Patient's and physician global assessment of pain, OA Severity Index and WOMAC OA Index Secondary: Safety	Primary: Celecoxib at BID doses of 100 and 200 mg was associated with a greater than 1-grade improvement in the patients global assessment and more than 30% reduction in pain severity ($P<0.05$). The 50-mg dose of celecoxib was submaximally effective compared with the 100-mg and 200-mg doses ($P<0.05$). The efficacy of the 100-mg dose was comparable to that of the 200-mg dose and were significantly superior to placebo ($P\leq0.05$). There was no difference in efficacy between the 100- and 200-mg doses of celecoxib when compared with naproxen (*P* value not reported). In the WOMAC OA Index composite score, changes from baseline for celecoxib at BID doses of 100 and 200 mg were twice as great as those for placebo treatment ($P\leq0.05$). Secondary: All 3 doses of celecoxib were well tolerated. Withdrawal and adverse events were similar between the celecoxib groups and placebo. The incidence of GI related adverse events was also similar across all treatment groups; 28%, 27%, and 24% for 50, 100, and 200 mg of celecoxib, respectively; 32% for naproxen; and 22% for placebo (*P* value not reported).
Stengaard-Pedersen et al[18] Celecoxib 200 mg QAM vs	DB, PC, RCT Patients at least 40 years old with clinical symptoms of OA according to American	N=697 12 weeks	Primary: Patient satisfaction assessment based on pain relief, ability to walk and	Primary: For the QAM vs QPM comparison, the 95% CIs were within the prespecified equivalence criteria for all three measures of patient satisfaction: pain relief, mean –0.2; 95% CI, –0.53 to 0.68; ability to walk and bend, mean –0.2; 95% CI, –0.54 to 0.64; willingness to continue medication, mean –0.7; 95% CI, –0.98 to 0.49 (*P* value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
celecoxib 200 mg QPM vs celecoxib 100 mg BID	College of Rheumatology classification in the hip or knee at least 3 months before randomization		bend at 12 weeks according to a 10 –point satisfaction scale (1=very dissatisfied and 10=very satisfied), willingness to continue with medication (also rated on a 10 point scale) Secondary: Physical function according to WOMAC OA Index and patients global assessment	The 95% CIs for the QD vs BID comparison were also within the –2 to +2 interval (*P* value not reported). Secondary: The mean improvement in WOMAC OA Index composite score was likewise similar across treatment groups. The least squares mean change was –11.19, –12.23 and –11.69 in the celecoxib 200 mg QAM, celecoxib 200 mg QPM and celecoxib 100 mg BID groups respectively (*P* value not reported). A similar proportion of patients in all three groups showed improvement (a reduction of at least two grades from baseline) in patient's global assessment of OA (11, 15 and 8% in the celecoxib 200 mg QAM group, celecoxib 200 mg QPM and celecoxib 100 mg BID group, respectively).
Whelton et al[19] Celecoxib 200 mg PO QD vs rofecoxib 25 mg PO QD	DB, DD, MC, PG, RCT Outpatients ≥65 years of age with stable, controlled hypertension; diagnosis of OA of the hip, knee or hand according to the American College of Rheumatology criteria and deemed to benefit from chronic daily therapy with an NSAID to control arthritis symptoms; patients were excluded if they had active GI	N=810 6 weeks	Primary: The development of edema, changes in systolic and diastolic blood pressure Secondary: Not reported	Primary: Nearly twice as many rofecoxib- compared with celecoxib-treated patients experienced edema (9.5% vs 4.9%; *P*=0.014). Systolic blood pressure increased significantly in 17% of rofecoxib compared with 11% of celecoxib-treated patients (*P*=0.032) at any study time point. Diastolic blood pressure increased in 2.3% of rofecoxib- compared with 1.5% of celecoxib-treated patients (*P*=0.44). At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with –0.5 mmHg for celecoxib (*P*=0.007). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	tract disease; renal, hepatic, or coagulation disorders; history of New York Heart Association Class III or IV heart failure; or secondary or malignant hypertension, or renal artery stenosis			
Singh et al[20] Celecoxib 100 mg BID vs celecoxib 200 mg BID vs diclofenac 50 mg BID or naproxen 500 mg BID	DB, MC Patients 18 years or older with OA of the hip, knee or hand for at least 6 months that required daily anti-inflammatory agents or analgesic therapy and a functional capacity classification ranging from I to III	N=13,274 12 weeks	Primary: Comparison of efficacy of management of signs/symptoms of OA of the hip, knee and hand as determined by VAS, Patient Global Assessment of Arthritis and total WOMAC OA Index Secondary: GI adverse effects and investigator-reported adverse events	Primary: It was noted that celecoxib 100 and 200 mg BID showed clinical efficacy comparable to naproxen and diclofenac for relief of the signs and symptoms of OA of the hip, knee and hand according to prespecified criteria (>10 mm difference on a 10-mm VAS; *P* value not reported). Secondary: Significantly more upper GI events were reported with the NSAID group compared to the celecoxib groups (95% CI, 1.50 to 34.57; *P*=0.004). Significantly more ulcer complications occurred within the NSAID group compared with celecoxib (95% CI, 1.46 to 33.80; *P*=0.008). There was no statistically significant difference between celecoxib and the NSAID group in any cardiovascular adverse event rate with the exception of investigator-reported cardiac failure (*P* values 0.11-1.0). The rate of cardiac failure was 0.22/100 patient-years with celecoxib and 1.00/100 patient-years with the NSAID group (95% CI, 1.26 to 20.06; *P*=0.01).
Silverstein et al[21] Celecoxib 400 mg BID vs	DB, MC, RCT Outpatients aged 18 years or older with diagnosis of RA or OA evident for at least 3	N=8,059 6 months	Primary: Incidence of prospectively defined symptomatic upper GI ulcers	Primary: For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% (*P*=0.09) and 2.08% vs 3.54% (*P*=0.02), respectively.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ibuprofen 800 mg TID vs diclofenac 75 mg BID Patients were allowed to take aspirin for cardioprotection.	months and expected to require continuous treatment with an NSAID for the duration of the trial		and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period Secondary: Not reported	For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% (*P*=0.04) and 1.40% vs 2.91% (*P*=0.02). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% (*P*=0.92) and 4.70% vs 6.00% (*P*=0.49). Fewer celecoxib treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use. Secondary: Not reported
Geba et al[10] Celecoxib 200 mg PO QD vs rofecoxib 12.5 mg PO QD vs rofecoxib 25 mg PO QD vs APAP 1,000 mg PO QID	CC, DB, MC, R Men and non-pregnant women greater ≥40 years of age with symptomatic OA of the knee for at least 6 months	N=382 6 weeks	Primary: Relief of pain on walking, night pain, pain at rest, and morning stiffness via the WOMAC OA Index over days 1 to 6 and over the entire 6-week period, global response to therapy Secondary: Safety , incidence of GI events and cardiac events	Primary: For pain on walking over the first 6 days of therapy, both doses of rofecoxib and the dose of celecoxib were found to be significantly better than APAP (-32.20, -29.00, -26.40 and -20.66 mm change on the VAS for rofecoxib 25 mg/day; *P*<0.001; rofecoxib 12.5 mg/day; *P*=0.004; and celecoxib; *P*=0.04 respectively). Over the entire 6-week period, the only statistically significant difference in pain on walking was between the APAP group (VAS change of -20.6 mm) and the rofecoxib 25 mg/day group (VAS change of -32.2 mm; *P*=0.001). For night pain, 25 mg/day of rofecoxib (-25.2 mm change in VAS) was found to be statistically better than celecoxib (-18.7 mm change in VAS); *P* =0.04) or APAP (-18.8 mm change in VAS; *P*=0.04) over the initial 6 days. The relief of rest pain was significantly improved over the 6-week period with 25 mg/day of rofecoxib (-21.8 mm change in VAS) compared with celecoxib (-15.5 mm change in VAS; *P*=0.02) or APAP (-12.5 mm change in VAS;

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				P=0.005). Rofecoxib 25 mg/day (-30.4 change in VAS) significantly improved morning stiffness compared with APAP (-12.5 change in VAS; *P*<0.04) over the 6-week trial. The percentage of patients who rated their global response as good or excellent was 60% in the rofecoxib 25-mg/day group, 56% in the rofecoxib 12.5-mg/day group, 46% in the celecoxib group, and 39% in the APAP group. A statistically better response to therapy was observed with 25 mg/day of rofecoxib compared with celecoxib (*P*=0.03) or APAP (*P*=0.003). Secondary: The APAP group had the largest percentage of withdrawals (31%) compared with the COX-2 inhibitors (18% to 19%). The incidence of GI events was similar among all groups. No myocardial infarctions were reported during the trial.
Schnitzer et al[22] Celecoxib 200 mg QD vs rofecoxib 12.5 mg QD vs rofexcoxib 25 mg QD vs APAP 4,000 mg (1,000 mg QID)	DB, MC, R Patients with OA	N=1,578 6 weeks	Primary: PGART, WOMAC OA Index Secondary: Adverse effects	Primary: Pooled analysis of VACT1/VACT2 studies demonstrated greater PGART (*P*=0.023) with rofecoxib 25 mg (56.1%) than celecoxib (49.8%) at 6 weeks and greater response to all other PGART and WOMAC endpoints, and confirmed superiority of COX-2 inhibitors to APAP. Secondary: Overall, tolerability of the study medications was generally good and similar. There was no significant difference between treatment groups in the percentage of patients who experienced a clinical adverse experience. The incidence of discontinuations due to a clinical adverse experience was significantly lower with celecoxib (2.5%) compared to rofecoxib 25 mg (6.3%; *P*=0.004) or APAP (7.8%; *P*<0.001), and did not differ significantly from rofecoxib 12.5 mg (4.6%). Discontinuation rates due to edema and hypertension related clinical adverse experiences were similar among all COX-2 inhibitors.

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Chan et al[23] Celecoxib 200 mg PO BID plus QD placebo vs diclofenac 75 mg BID plus omeprazole 20 mg QD	DB, PC, RCT Helicobacter pylori negative patients who used NSAIDs for arthritis and who presented with ulcer bleeding	N=287 6 months	Primary: Recurrent ulcer bleeding Secondary: Adverse events	Primary: Recurrent ulcer bleeding occurred in 7 patients receiving celecoxib and 9 receiving diclofenac plus omeprazole. The probability of recurrent bleeding during the six-month period was 4.9 percent (95% CI, 3.1 to 6.7) for patients who received celecoxib and 6.4% (95% CI, 4.3 to 8.4) for patients who received diclofenac plus omeprazole (difference, -1.5 percentage points; 95% CI, -6.8 to 3.8). Secondary: Renal adverse events, including hypertension, peripheral edema, and renal failure, occurred in 24.3% of the patients receiving celecoxib and 30.8% of those receiving diclofenac plus omeprazole.
Rheumatoid Arthritis				
Emery et al[11] Celecoxib 200 mg PO BID vs diclofenac 75 mg PO BID	DB, DD, PG, MC Patients with diagnosis of adult-onset RA of at least 6 months' duration, according to American Rheumatism Association criteria, a functional capacity classification of III or less, and were anticipated to require continuous treatment with an NSAID for the duration of the trial	N=655 24 weeks	Primary: Patients and physicians assessments, number of swollen joints, and number of tender/painful joints and GI safety based on a single upper GI endoscopy at week 24 Secondary: Number of patients responding according to the American College of Rheumatology - 10 Index	Primary: Celecoxib and diclofenac did not differ for almost all measures of pain and inflammation associated with RA, or for distribution of patients classified by change in RA disease status on global assessment of arthritis condition. The mean number of tender or painful or swollen joints decreased over time in the two groups. The difference between treatment groups was not significant at any time, apart from week 16, when the number of tender or painful joints was significantly lower in the celecoxib treatment group. (P<0.05). There were significantly more gastro-duodenal ulcers in the group receiving diclofenac than in the celecoxib arm (34% vs 18%; P<0.001). GI-related adverse events occurred in 48% of those taking diclofenac and 36% of those taking celecoxib (P<0.05). The rate of withdrawal because of GI adverse effects was 16% for diclofenac versus 6% for celecoxib (P<0.001).

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				Secondary: 80 (25%) patients in the celecoxib group and 73 (22%) patients in the diclofenac group showed improvement on the American College of Rheumatology-10 responder index at week 24.
Simon et al[12] Celecoxib 100 mg PO BID vs celecoxib 200 mg PO BID vs celecoxib 400 mg PO BID vs naproxen 500 mg PO BID vs placebo	DB, MC, PC, RCT Outpatients aged 18 years or older who fulfilled the American College of Rheumatology criteria for a diagnosis of RA evident for 3 months or longer and were in a functional class of I, II, or III	N=1,149 12 weeks	Primary: Improvement in signs and symptoms of RA as assessed using standard measures of efficacy Secondary: GI tract safety as assessed by upper GI tract endoscopy before and after treatment	Primary: Patient's global assessments found all doses of celecoxib to be superior to placebo, although the 100-mg dose was not found to be significantly better than placebo in the physician's global assessments. The 200-mg dose was found to be significantly better than naproxen only in the patient's and physician's global assessments (P<0.05). All other celecoxib doses had results comparable to those of naproxen in all measures. Secondary: Adverse GI effects were reported in 19% of placebo patients; 28%, 25%, and 26% of the patients receiving 100-, 200-, and 400-mg doses of celecoxib, and 31% of naproxen patients. Overall incidence of gastro-duodenal ulcers was 26% for naproxen, 6% for 400 mg of celecoxib, 4% for 200 mg of celecoxib, 6% for 100 mg of celecoxib, and 4% for placebo. Endoscopically documented gastro-duodenal ulcers were found to be significantly higher in the naproxen arm (P<0.001).
Pain				
Meunier et al[24] Celecoxib 200 mg 1 hour preoperatively, then BID for 3 weeks vs	DB, PC, RCT Patients 50 to 80 years of age, undergoing total knee replacement	N=50 12 months	Primary: Pain intensity (as rated on a VAS, ROM, KOOS), blood loss after surgery based on Hb balance	Primary: VAS pain scores were similar between the two groups preoperatively and during hospital stay, but became lower in the celecoxib group at 14 days post surgery. There were no statistically significant differences in ROM between both groups. There was no difference in KOOS scores throughout the 12 month

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placebo			Secondary: Opioid consumption	period. Total blood loss was similar between each group (0.7 to 0.8 L). No patient received a blood transfusion postoperatively. Secondary: Less analgesic medication was consumed in the group treated with celecoxib compared to the control group (6 mg vs 10 mg). There was also lower tramadol consumption during the first 3 weeks after surgery (2.4 g vs 3.4 g; CI, -3.0 to 2.2).
Reuben et al[13] Celecoxib 200 mg vs rofecoxib 50 mg vs placebo Study medications were administered 1 hour before induction of anesthesia.	CC, DB, PC, R Patients 18 years old, ≥40 kg, who could operate a PCA, scheduled to undergo elective decompressive lumbar laminectomy with spinal fusion by a single surgeon	N=60 24 hours	Primary: Opioid sparing effects, duration of analgesia, reduction in morphine use Secondary: Not reported	Primary: Use of rofecoxib or celecoxib resulted in a significant opioid-sparing effect compared with placebo (*P*<0.0001). Rofecoxib was associated with a significantly greater duration of analgesic activity throughout the 24- hour study period. Celecoxib was associated with a reduced amount of morphine use for only the 0- to 8-hour post surgery period. Secondary: Not reported
Malmstrom et al[25] Celecoxib 200 mg vs rofecoxib 50 mg vs	CC, DB, DD, PC, PG, R Patients with postoperative dental pain	N=544 24 hours	Primary: Analgesic activity Secondary: Adverse events	Primary: There was a significantly greater analgesic activity in patients who received rofecoxib vs celecoxib or placebo (*P*<0.001). Analgesic effects of rofecoxib were observed to be similar to those of ibuprofen (*P*=0.46). The analgesic advantage of rofecoxib over celecoxib and placebo was noted as well (*P*<0.001). Onset of pain relief was achieved significantly faster with rofecoxib than with celecoxib (30 minutes vs 1 hour; *P*<0.05). The onset of analgesia was not

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ibuprofen 400 mg vs placebo Patients received a single-dose and were observed for 24 hours.				significantly different between rofecoxib and ibuprofen. In addition, rofecoxib resulted in a significantly greater duration of analgesic effect at 24 hours compared with celecoxib and ibuprofen (*P*<0.001). Secondary: The most commonly reported adverse events in all groups included nausea, headache, and vomiting.
Doyle et al[26] Celecoxib 200 mg (baseline, followed by placebo at 4 and 8 hours) vs ibuprofen 400 mg (baseline, then at 4 and 8 hours) vs placebo	DB, DD, MD, PC, PG, R Patients scheduled to undergo surgical removal of one or more impacted third molars	N=179 12 hours	Primary: Pain relief plus pain intensity difference Secondary: Tolerability	Primary: The study demonstrated assay sensitivity in that both active medications were more effective than placebo for all efficacy measures (*P*<0.001). In comparing the two active medications, the time to meaningful relief was shorter, and the mean 4-, 8-, and 12-hour summed pain relief combined with pain intensity difference scores were significantly higher for ibuprofen liquid-gels compared with celecoxib (*P*<0.001). Analyses of other key efficacy variables, including the time to rescue medication (*P*<0.05) and the patients' overall assessment of study medication (*P*<0.001), confirmed the superior efficacy of ibuprofen liquid-gels over celecoxib. Secondary: Both active treatments were well tolerated, with no differences in incidence or severity of adverse events. Of particular interest, there were no differences in GI-related side effects when comparing these doses of to celecoxib.
Loo et al[27] Celecoxib 400 mg at onset of attack vs naproxen sodium 550 mg at onset of attack	OL, RCT Patients 18 years and older who had disease duration of at least 6 months and a migraine attack frequency of at least twice per month over the past 6 months	N=52 1 month	Primary: Severity in attack baseline, one hours, two hours and four weeks following medication ingestion (VAS)	Primary: VAS of each treatment group were unable to show any significant difference in migraine improvement at baseline (*P*=0.410) and at baseline to two hours (*P*=0.407). In the celecoxib group, the VAS was 6.48+1.53 at baseline, 4.28+2.11 at one hour, and 2.24+2.57 at two hours. In the naproxen sodium group, the VAS at baseline, one hour and two hours were 7.30+1.66, 4.81+2.50, and 2.63+2.65, respectively.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Occurrence of adverse effects	Secondary: The most common adverse effects reported by patients were epigastric pain, nausea, numbness and insomnia. Epigastric pain was the only adverse effect that occurred significantly more often in the naproxen sodium group (*P*=0.029).
Gimbel et al[28] Single-dose assessment period (pain assessments conducted over the following 8 hours): Celecoxib 200 mg plus hydrocodone 10 mg/APAP 1,000 mg or placebo Multiple-dose assessment period (pain assessments following the 8 hour period up to 5 days): celecoxib 200 mg plus hydrocodone 10 mg/ APAP 1,000 mg or placebo TID PRN Two studies with identical protocols were combined.	CC, DB, PC, PG, R Patients with acute pain after orthopedic surgery	N=418 5 days	Primary: Rescue medication, analgesic effects, pain intensity scores Secondary: Adverse events	Primary: In the single-dose assessment period, comparable analgesic effects were noted between celecoxib and placebo versus celecoxib plus hydrocodone/APAP. In the multidose assessment period, celecoxib TID as needed was observed to result in superior analgesic effects compared with hydrocodone/ APAP. Patients in the celecoxib group of the multidose assessment period required less rescue medication (20% vs 12%; *P*<0.05), had lower maximum pain intensity scores (*P*<0.001), took fewer doses of medication (*P*≤0.001), and had better pain scores (*P*≤0.013). Secondary: The celecoxib group had the highest percentage of patients experiencing ≥1 adverse event: 11% for celecoxib; 14% for placebo; 27% for hydrocodone/ APAP (*P*=0.002).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Salo et al[29] Celecoxib 200 mg QD vs celecoxib 400 mg QD vs ibuprofen 600 mg QD	DB, PRO, RCT Patients with acute pain	N=105 5 hours	Primary: VAS, categorical intensity pain scale Secondary: Not reported	Primary: There was no statistical difference among the treatment groups in age, time from injury to medication, initial VAS score, % lost to follow-up, or treatment with adjunctive therapy. There was no statistical difference in change of VAS among the groups at five hours (*P*=0.16). There was no significant difference between the groups, at five hours, in change of categorical pain intensity (*P*=0.11) or pain relief scores (*P*=0.059), though the pain relief scale approached significance favoring ibuprofen. Secondary: Not reported
Familial Adenomatous Polyposis				
Arber et al[30] Celecoxib 400 mg QD vs placebo	DB, MC, PC, R Patients that had adenomas removed prior to enrollment	N=1,738 3 years	Primary: Detection by colonoscopy of at least one colorectal adenoma Secondary: Number of colorectal adenomas, size of the largest ones, total adenoma burden	Primary: Colonoscopies were performed at year 1 on 88.7% of the subjects who had undergone randomization and at year 3 on 79.2%. Of the 557 subjects in the placebo group and the 840 subjects in the celecoxib group who were included in the efficacy analysis, 264 and 270, respectively, were found to have at least one adenoma at year 1, at year 3, or both. The cumulative rate of adenomas detected through year 3 was 33.6% in the celecoxib group and 49.3% in the placebo group (RR, 0.64; 95% CI, 0.56 to 0.75; *P*<0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3% in the celecoxib group and 10.4% in the placebo group (RR, 0.49; 95% CI, 0.33 to 0.73; *P*<0.001). Adjudicated serious cardiovascular events occurred in 2.5% of subjects in the celecoxib group and 1.9% of those in the placebo group (RR, 1.30; 95% CI, 0.65 to 2.62). Secondary: Among subjects who had any new adenoma detected, the mean size of the largest adenoma and the mean adenoma burden were significantly lower in

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the celecoxib group than in the placebo group (*P*=0.002 and *P*=0.005 respectively); the difference in the mean number of adenomas was not significant (*P*=0.15).
Steinbach et al[15] Celecoxib 100 mg BID vs celecoxib 400 mg BID vs placebo	DB, PC, RCT Patients with familial adenomatous polyposis who were 18 to 65 years of age, who had not had their entire colorectum removed, and who had five or more polyps 2 mm or more in diameter that could be assessed endoscopically	N=77 6 months	Primary: Percent reduction in the mean number of colorectal polyps and percent reduction in the polyp burden (the sum of polyp diameters) Secondary: The improvement in the extent of colorectal polyposis	Primary: Treatment with 400 mg of celecoxib BID for six months was associated with a significant reduction from base line in the number of colorectal polyps as compared with the placebo group (28.0% vs 4.5%; *P*=0.003). The group receiving 100 mg of celecoxib BID had a reduction of 11.9% as compared with 4.5% in the placebo group (*P*=0.33). The average decreases in polyp burden were 30.7% for the group receiving 400 mg of celecoxib BID, 14.6% for the group receiving 100 mg of celecoxib BID, and 4.9% for the placebo group (*P*=0.001 for the comparison of 400 mg of celecoxib BID and placebo). Secondary: The group receiving 400 mg of celecoxib BID, significant improvement in polyposis occurred in the rectum (*P*=0.01), in the ascending colon and cecum (*P*=0.02), and in the transverse, descending, and sigmoid colon (*P*=0.003). The corresponding changes in the group receiving 100 mg of celecoxib BID were not significant, but there was a trend toward a dose response in the rectum (*P*=0.07) and in the ascending colon and cecum (*P*=0.10).
Phillips et al[16] Celecoxib 100 mg BID vs celecoxib 400 mg BID vs placebo	DB, PC, RCT Patients with a retained colonic or rectal remnant containing a minimum of five adenomas	N=83 6 months	Primary: Change in area of duodenal polyposis from baseline Secondary: Adverse effects	Primary: Celecoxib 400 mg BID showed a statistically significant reduction in adenoma size versus placebo (mean change -30.6 vs 8.3; *P*=0.049). Celecoxib 100 mg BID did not show a significant reduction versus placebo (mean change -26.6 vs 8.3; *P*=0.252). Secondary: Celecoxib 100 and 400 mg BID were reported to be safe and well tolerated. One patient taking celecoxib 400 mg BID experienced an allergic reaction and

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				withdrew from the study as a result. Another patient taking celecoxib 400 mg BID withdrew from the study due to dyspepsia. A patient taking celecoxib 100 mg BID with a history of psychosocial and emotional problems, committed suicide during the study.
Solomon et al[31] Celecoxib 200 mg PO BID vs celecoxib 100 mg PO BID vs placebo	DB, MC, PC, RCT Patients 32 to 88 years of age considered to have a clinically significant risk of colorectal adenoma on the basis of a history of either multiple adenomas or a single adenoma that was at least 0.5 cm in diameter	N=2,035 3 years	Primary: Incidence of potentially serious cardiovascular events (defined by a composite cardiovascular end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure) Secondary: Not reported	Primary: The composite cardiovascular endpoint was reached in 7 of 679 patients in the placebo group (1.0%), as compared with 16 of 685 patients receiving 200 mg of celecoxib BID (2.3%; HR, 2.3; 95% CI, 0.9 to 5.5) and with 23 of 671 patients receiving 400 mg of celecoxib BID (3.4%; HR, 3.4; 95% CI, 1.4 to 7.8; *P* values not reported). On the basis of these observations, the data and safety monitoring board recommended early discontinuation of the study drug. Secondary: Not reported
Solomon et al[32] Adenoma Prevention With Celecoxib (APC)[31] Celecoxib 400 mg PO BID vs celecoxib 200 mg PO BID Prevention of	DB, MC, PC, R Patient data from APC[31] and PreSap[30] were combined	N=3,773 3 years	Primary: Cardiovascular endpoints Secondary: Not reported	Primary: For adjudicated cardiovascular events, 77% and 54% in APC and PreSAP, respectively, had 37 months of follow-up. For APC and PreSAP combined, 83 patients experienced cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure. The hazard ratio for this prespecified composite end point was 2.6 (95% CI, 1.1 to 6.1) in patients taking 200 mg BID, 3.4 (95% CI, 1.5 to 7.9) in patients taking 400 mg BID in APC, and 1.3 (95% CI, 0.6 to 2.6) in patients taking 400 mg QD in PreSAP (*P*=0.13 comparing the combined doses in APC with the dose in PreSAP). The overall hazard ratio for this composite end point was 1.9 (95% CI, 1.1 to 3.1). Both dose groups in APC showed significant systolic blood pressure

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Spontaneous Adenomatous Polyps (PreSap)[30] Celecoxib 400 mg PO QD vs placebo				elevations at 1 and 3 years (200 mg BID: 1 year, 2.0 mm Hg; 3 years, 2.6 mm Hg; 400 mg BID: 1 year, 2.9 mm Hg; 3 years, 5.2 mm Hg); however, the 400 mg QD group in PreSAP did not (*P*<0.0001 between studies). Secondary: Not reported
Ankylosing Spondylitis				
Dougados et al[33] Celecoxib 100 mg PO BID vs ketoprofen 100 mg PO BID vs placebo	DB, PC, RCT Patients were included if they had ankylosing spondylitis according to the modified New York criteria, without peripheral synovitis and with active disease (pain >40 mm on a 100-mm VAS and an increase in pain of at least 30% after NSAID withdrawal)	N=246 6 weeks	Primary: Change in pain intensity (VAS) and change in functional impairment (BASFI) Secondary: Epigastric pain	Primary: Decrease in pain and functional impairment was greater in the active treatment groups than in the placebo group, with a trend in favor of celecoxib when the 2 active treatments were compared. The mean changes were -13 mm, -21 mm, and -27 mm (*P*=0.006) for pain and 1, -6, and -12 (*P*=0.0008) for BASFI score in the placebo, ketoprofen, and celecoxib groups, respectively. Secondary: During treatment, the number of patients reporting epigastric pain was 6 (8%), 13 (14%), and 10 (13%) in the placebo, ketoprofen, and celecoxib groups, respectively.
Sieper et al[34] Celecoxib 200 mg QD vs celecoxib 200 mg BID vs	DB, MC, RCT Patients ages 18 to 75 with a confirmed diagnosis of ankylosing spondylitis according to the modified New York criteria, the presence of axial involvement, absence of peripheral	N=458 12 weeks	Primary: Change from baseline in global pain intensity on a VAS at week 12 Secondary: Changes in disease activity and both,	Primary: There was a clinically relevant decrease in the mean VAS score over the treatment period of 12-weeks in all treatment groups by -29.1 mm on celecoxib 200 mg QD (95% CI, -33.6 to -24.6), -31.7 mm on celecoxib 200 mg BID (95% CI, -36.2 to -27.2), and -32.7 on diclofenac (95% CI, -37.1 to -29.2). Both dosages of celecoxib proved superior to diclofenac administration. Secondary: Ankylosing Spondylitis Assessment Study group 20% response and mean improvement in Bath Ankylosing Spondylitis Disease Activity Index scores at

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diclofenac sustained release 75 mg BID	involvement and the need for daily NSAID treatment		functional and mobile capacities, adverse events	week 12 were numerically better on celecoxib 200 mg BID (59.7% and –1.32 points) and on diclofenac (60.2% and –1.48 points) than on celecoxib 200 mg QD (46.0% and –0.99 points). A total of 251 patients (54.8%) experienced treatment emergent adverse effects. Serious adverse effects in the group receiving celecoxib 200 mg BID included angina pectoris, dyspnea, and sudden hearing loss. Serious adverse effects in the diclofenac group included myocardial infarction and tinnitus.

Drug regimen abbreviations: BID=twice daily, PO=by mouth, PRN=as needed, QD=once daily, QAM=once daily in the morning, QID=four times daily, QPM=once daily in the evening, TID=three times daily
Study abbreviations: CI=confidence interval, CC=comparator controlled, DB=double blind, DD=double dummy, HR=hazard ratio, MC=multicenter, MD=multiple dose, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: APAP=acetaminophen, BASFI=Bath Ankylosing Spondylitis Functional Index, COX=cyclooxygenase, GI=gastrointestinal, Hb=hemoglobin, KOOS=osteoarthritis outcome score, NSAIDS=nonsteroidal anti-inflammatory drugs, OA=osteoarthritis, PCA=patient-controlled analgesia, PGART=Patient Global Assessment of Response to Therapy, RA=Rheumatoid Arthritis, ROM=range of knee motion, VAS=visual analog scale, WOMAC OA Index=OA Severity index and Wester Onterio and McMaster University physical functioning and joint stiffness subscales

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Special Populations

Table 5. Special Populations[7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Celecoxib	Dose adjustment is usually not necessary in elderly patients. Elderly patients weighing less than 50 kg, initiate therapy at the lowest recommended dosage. Safety and efficacy has been established only in children 2 years of age or older and for a maximum of 6 months of treatment in juvenile rheumatoid arthritis. Safety and efficacy has not been established in children for any other indication.	Not recommended in patients with advanced renal disease. If treatment with celecoxib is necessary, monitor patients renal function closely.	The daily dose of celecoxib should be reduced by 50% in patients with moderate hepatic impairment. Celecoxib is not recommended for patients with severe hepatic impairment.	C	Limited data (included a total of 12 breastfeeding women) showed low levels of celecoxib in breast milk. Caution should be exercised when celecoxib is administered to a nursing woman.

Adverse Drug Events

The most common adverse drug events reported with celecoxib are noted in Table 6.

Table 6. Adverse Drug Events (%)[7]

Adverse Event	Celecoxib
Cardiovascular	
Aggravated hypertension	✔
Angina pectoris	✔
Coronary artery disorder	✔
Myocardial infarction	✔
Palpitation	✔
Tachycardia	✔
Central and Peripheral Nervous System	
Dizziness	2
Headache	15.8
Hypertonia	✔
Hypoesthesia	✔
Migraine	✔
Neuralgia	✔
Neuropathy	✔
Leg cramps	✔
Paresthesia	✔
Vertigo	✔
Dermatological	
Alopecia	✔

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Adverse Event	Celecoxib
Cellulitis	✔
Dermatitis	✔
Photosensitivity reaction	✔
Pruritis	✔
Rash	2.2
Rash erythematous	✔
Rash maculopapular	✔
Skin disorder	✔
Skin dry	✔
Sweating increased	✔
Urticaria	✔
Endocrine and Metabolic	
Diabetes mellitus	✔
Edema	✔
Hypercholesterolemia	✔
Hyperglycemia	✔
Peripheral edema	2.1
Weight increase	✔
Gastrointestinal	
Abdominal pain	4.1
Constipation	✔
Diarrhea	5.6
Diverticulitis	✔
Dry mouth	✔
Dyspepsia	8.8
Dysphagia	✔
Eructation	✔
Esophagitis	✔
Flatulence	2.2
Gastritis	✔
Gastroenteritis	✔
Gastroesophageal reflux	✔
Hemorrhoids	✔
Hiatal hernia	✔
Melena	✔
Nausea	3.5
Stomatitis	✔
Tenesmus	✔
Tooth disorder	✔
Vomiting	✔
Genitourinary	
Dysmenorrhea	✔
Menstrual disorder	✔
Prostatic disorder	✔
Vaginal hemorrhage	✔
Vaginitis	✔
Hematologic	
Anemia	✔
Thrombocythemia	✔
Hepatic	
Hepatic function abnormal	✔

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Adverse Event	Celecoxib
Lab Test Abnormalities	
Elevated alkaline phosphatase	✔
Elevated blood urea nitrogen	✔
Elevated creatinine	✔
Elevated creatine phosphokinase	✔
Elevated serum glutamic oxaloacetic transaminase	✔
Elevated serum glutamic pyruvic transaminase	✔
Hypokalemia	✔
Musculoskeletal	
Arthralgia	✔
Arthrosis	✔
Myalgia	✔
Synovitis	✔
Tendinitis	✔
Ocular	
Blurred vision	✔
Cataract	✔
Conjunctivitis	✔
Eye pain	✔
Glaucoma	✔
Otic	
Deafness	✔
Ear abnormality	✔
Earache	✔
Otitis media	✔
Tinnitus	✔
Psychiatric	
Anorexia	✔
Anxiety	✔
Appetite increased	✔
Depression	✔
Insomnia	2.3
Nervousness	✔
Somnolence	✔
Renal	
Albuminuria	✔
Cystitis	✔
Dysuria	✔
Hematuria	✔
Micturition frequency	✔
Renal calculus	✔
Respiratory	
Bronchitis	✔
Bronchospasm aggravated	✔
Coughing	✔
Dyspnea	✔
Laryngitis	✔
Pharyngitis	2.3
Pneumonia	✔
Rhinitis	2
Sinusitis	5

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Adverse Event	Celecoxib
Upper respiratory tract infection	8.1
Other	
Allergy aggravated	✔
Allergic reaction	✔
Asthenia	✔
Breast fibroadenosis	✔
Breast neoplasm	✔
Breast pain	✔
Chest pain	✔
Ecchymosis	✔
Epistaxis	✔
Face edema	✔
Fatigue	✔
Fever	✔
Herpes simplex	✔
Herpes zoster	✔
Hot flushes	✔
Injury, accidental	2.9
Infection bacterial	✔
Infection fungal	✔
Infection soft tissue	✔
Infection viral	✔
Influenza-like symptoms	✔
Moniliasis	✔
Moniliasis genital	✔
Pain	✔
Peripheral pain	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications / Precautions[7]

Celecoxib is contraindicated in patients with known hypersensitivity to celecoxib. Celecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides. Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients. Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Celecoxib cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The concomitant use of celecoxib with any dose of a non-aspirin NSAID should be avoided. The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Borderline elevations of one or more liver associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib. A patient with symptoms and/or signs

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suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), celecoxib should be discontinued.

Anemia is sometimes seen in patients receiving celecoxib. Patients on long-term treatment with celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages. Celecoxib should be used only with caution in pediatric patients with systemic onset juvenile rheumatoid arthritis (JRA) due to the risk for serious adverse reactions including disseminated intravascular coagulation.

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, celecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

In 2005, the manufacturers of celecoxib were asked by the Food and Drug Administration (FDA) to revise the product labeling and include a boxed warning, highlighting the potential for increased risk of cardiovascular events and serious, potential life-threatening gastrointestinal bleeding associated with its use. Celecoxib is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery.[9]

Black Box Warning for Celecoxib and Cardiovascular Risk[7]

Warning for Cardiovascular Risk
Cardiovascular Risk CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal anti-inflammatory drugs (NSAIDs) may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. CELEBREX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Black Box Warning for Celecoxib and Gastrointestinal Risk[7]

Warning for Gastrointestinal Risk
Gastrointestinal Risk NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Drug Interactions

Celecoxib shares many of the same interactions seen with other nonsteroidal anti-inflammatory drugs (NSAIDs). Most traditional NSAIDs inhibit platelet aggregation and have adverse effects on the gastrointestinal mucosa. Unlike traditional NSAIDs, celecoxib has little or no effect on platelet aggregation and a lower propensity to cause severe gastrointestinal toxicity. Despite these potentially positive attributes, caution should be used when these agents are coadministered with warfarin, and scheduled monitoring of the international normalized ratio (INR) should occur when celecoxib therapy is initiated or

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changed, particularly during the first several days of concomitant therapy. The initial prescribing information for celecoxib stated that it did not alter the anticoagulant effect of warfarin as determined by prothrombin time.[35] However, there have been post marketing reports of increased prothrombin time and INR values when celecoxib and warfarin were administered concomitantly.[36-38] This effect is sometimes associated with bleeding events and occurs predominantly in older people. The prescribing information for celecoxib now also advises that anticoagulation activity be monitored, particularly during the first few days after initiating or changing celecoxib therapy. In addition, a case report documented an intracerebral hemorrhage in a patient who had been administered concomitant celecoxib and clopidogrel, reinforcing the need for caution when celecoxib is used with an agent that affects platelets.[39] Significant drug interactions with celecoxib are listed in Table 7.

Table 7. Drug Interactions[7,8]

Generic Name	Interacting Medication or Disease	Potential Result
Celecoxib	Angiotensin II antagonists	Reports suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors and angiotensin II antagonists.
Celecoxib	ACE inhibitors	Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors and angiotensin II antagonists.
Celecoxib	Aspirin	Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with celecoxib increases the rate of gastrointestinal ulceration or other complications, compared to use of celecoxib alone.
Celecoxib	Fluconazole	Concomitant administration of fluconazole at 200 mg daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole. Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.
Celecoxib	Furosemide	Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.
Celecoxib	Lithium	In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with celecoxib 200 mg twice daily as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.
Celecoxib	Methotrexate	In an interaction study of rheumatoid arthritis patients taking methotrexate, celecoxib did not have a significant effect on the pharmacokinetics of methotrexate.
Celecoxib	Warfarin	Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the

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Generic Name	Interacting Medication or Disease	Potential Result
		elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin.

Dosage and Administration

Use the lowest effective dose of celecoxib for the shortest duration consistent with treatment goals for the individual patient. These doses can be given without regard to timing of meals. The daily recommended dose of celecoxib capsules in patients with moderate hepatic impairment should be reduced by 50%. The use of celecoxib in patients with severe hepatic impairment is not recommended.[7] Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers. Consider using alternative management in juvenile rheumatoid arthritis patients who are poor metabolizers.[7] The usual dosing regimens for celecoxib are summarized in Table 8.

Table 8. Dosing and Administration[7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Celecoxib	Osteoarthritis: 200 mg once daily or 100 mg twice daily Rheumatoid arthritis: 100 to 200 mg twice daily Ankylosing spondylitis: 200 mg once daily in a single dose or 100 mg twice daily; if no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit Acute pain and primary dysmenorrheal: 400 mg initially, followed by 200 mg dose if needed on first day; on subsequent days, 200 mg twice daily as needed Familial adenomatous polyposis: 400 mg twice daily with food, as an adjunct to usual care	Juvenile Rheumatoid Arthritis: Patients age 2 years and older >10 kg to <25 kg, 50 mg twice daily Patients age 2 years and older >25 kg, 100 mg twice daily	Capsule: 50 mg 100 mg 200 mg 400 mg

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Assessments in Ankylosing Spondylitis (ASAS) Working Group: **International ASAS Consensus Statement for the Use of Anti-tumor Necrosis Factor Agents in Patients with Ankylosing Spondylitis (2003)[40]**	• Conventional therapies include: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, sulfasalazine for peripheral arthritis, and methotrexate (however, there is no evidence of benefit). • Patients who have an inadequate response to NSAIDs are candidates for anti-(tumor necrosis factor α (TNFα) therapy. • Failure is defined as a trial of 2 different NSAIDs at adequate doses for at least 3 months. • The role of cyclooxygenase (COX)-2 inhibitors was not addressed in this guideline.

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Clinical Guideline	Recommendations
American Society of Colon and Rectal Surgeons: **Practice Parameters for the Treatment of Patients with Dominantly Inherited Colorectal Cancer (2003)**[41]	Familial Adenomatous Polyposis (FAP) • Treatment must be preceded by thorough counseling about the nature of the syndrome, its natural history, its extra colonic manifestations, and the need for compliance with recommendations for management and surveillance. • Use of chemoprevention as primary therapy for colorectal polyposis is not proven and is not recommended. • Treatment of duodenal adenomas depends on adenoma size and the presence of severe dysplasia. Small tubular adenomas with mild dysplasia can be kept under surveillance, but adenomas with severe dysplasia must be removed. • Intra-abdominal desmoid tumors involving the small bowel mesentery are treated according to their rate of growth and their presentation. Clinically inert tumors should be treated with sulindac or not treated at all. Slowly growing or mildly symptomatic tumors may be treated with less toxic regimens such as sulindac and tamoxifen or vinblastine and methotrexate. Rapidly growing tumors need aggressive therapy with either very high-dose tamoxifen or anti-sarcoma-type chemotherapy. • Radiation is an option if collateral damage is not a big concern. • The role of COX-2 inhibitors was not addressed in this guideline.
Cleveland Clinic: **Medical Treatment of Juvenile Idiopathic Arthritis (2005)**[42]	Oligoarthritis • Approximately 1⁄4 to1⁄3 of patients will respond to NSAID therapy. • Intra-articular corticosteroid injections (e.g. triamcinolone hexacetonide) are effective in patients not responsive to NSAIDs after 4 to 6 weeks. • Patient's not responsive to corticosteroid injections or with extended oligoarthritis or small joint involvement should be treated as patients with polyarthritis. Polyarthritis, Rheumatoid Factor Negative • NSAIDs are mostly not effective as disease-modifying medications. NSAIDs should be used for symptom control and should not be used as monotherapy if not effective after several weeks. • Methotrexate should be administered parenterally and started early, initially at 10 mg/m^2 per week, and increased to 15 mg/m^2 per week if not effective at initial dose. • Alternatives include sulfasalazine and leflunomide. If not effective, anti-TNFα medications should be used. Intra-articular corticosteroid injections can be used as an adjunct for single or a few painful or swollen joints. • Systemic corticosteroids may be used as a bridging medication or during flares. Polyarthritis, Rheumatoid Factor Positive • These patients have a poor prognosis and should be treated aggressively per algorithms for rheumatoid arthritis in adults, including the early use of methotrexate and addition of anti-TNFα medications in patients with an inadequate response to methotrexate.

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Clinical Guideline	Recommendations
	Systemic Arthritis • There is a lack of evidence for systemic arthritis treatment. • NSAIDs and systemic corticosteroids are options for symptomatic relief (fever, serositis). • Intra-articular corticosteroid injections, methotrexate, and anti-TNFα medications appear to be less beneficial than in other subtypes of Juvenile Idiopathic Arthritis. Enthesitis-Related Arthritis • There is little evidence-based medicine for this form of Juvenile Idiopathic Arthritis. • Sulfasalazine may be beneficial (particularly for boys aged 9 years or older with peripheral arthritis). • Anti-TNFα medications are highly effective. Psoriatic Arthritis • There are no studies evaluating treatment in children. • The presentation of psoriatic arthritis can include oligoarthritis, polyarthritis and enthesitis-related arthritis. Treatment should parallel the treatment of that Juvenile Idiopathic Arthritis. • The role of COX-2 inhibitors was not addressed in this guideline.
American College of Rheumatology Subcommittee on Osteoarthritis: **Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee (2000)**[43]	• The goals of management of patients with osteoarthritis include control of pain and improvement in function and health-related quality of life, with avoidance of toxic effects of therapy. • Drug therapy for pain management is most effective when combined with nonpharmacologic strategies, therefore nonpharmalogical therapies should be maintained throughout treatment. Nonpharmacological Therapy • Patient and family/caregiver education, participation in self-management programs and personalized social support are recommended to improve outcomes. • Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. • Quadriceps strengthening and aerobic exercise are recommended for patients with knee osteoarthritis. • Weight loss is recommended in patients with knee and hip osteoarthritis. • Assistive devices for ambulation, patellar taping, appropriate footwear, bracing and assistive devices may help improve mobility and activities of daily living. Pharmacological Therapy • Relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen (APAP), is comparable with that achievable with an NSAID • In individuals with osteoarthritis of the knee who have mild-to-moderate pain, do not respond to APAP, and do not wish to take systemic therapy, the use of topical analgesics (e.g., methyl salicylate or capsaicin cream) is appropriate as either adjunctive

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Clinical Guideline	Recommendations
	treatment or monotherapy. • The options for medical management of osteoarthritis that has not responded to APAP or topical agents in patients who are at increased risk for a serious upper gastrointestinal adverse event, such as bleeding, perforation, or obstruction, include COX-2 inhibitors, a nonselective NSAID plus misoprostol or a proton pump inhibitor, nonacetylated salicylate , or local intraarticular therapy. • Celecoxib has been found to be more effective than placebo and comparable in efficacy with naproxen in patients with hip or knee osteoarthritis. • Of further advantage with respect to upper gastrointestinal bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation nor bleeding time. • Coxibs are an alternative to nonselective NSAIDs in patients at risk of developing gastrointestinal toxicity associated with NSAID therapy. • Additionally, at doses recommended for treatment of osteoarthritis, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of dyspepsia and other gastrointestinal side effects, than comparator nonselective NSAIDs. • Tramadol, a centrally acting opioid agonist, can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function or in patients who have not responded to previous oral therapy. • More potent opioid therapy can be considered in patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain. • It is reasonable to use the recommended agents in combination. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81-325 mg/day) with other NSAIDs.
American Academy of Orthopedic Surgeons (AAOS): **Clinical Practice Guideline on Osteoarthritis of the Knee (2008)**[44]	Nonpharmacological/Surgical Therapy • Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening. • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose body.

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<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>Pharmacological Therapy
• Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee.
• Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment:
o APAP (not to exceed 4 grams per day)
o NSAIDs
• Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain:
o APAP (not to exceed 4 grams per day)
o Topical NSAIDs
o Nonselective oral NSAIDs plus gastro-protective agent
o COX-2 inhibitors
• Intra-articular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee.</td></tr>
<tr><td>Treatment Guidelines from The Medical Letter:
Drugs for Pain (2007)[45]</td><td>• Aspirin, APAP, and NSAIDS are recommended as first line agents for mild to moderate pain.
• For moderate pain, NSAIDS have been shown to be more effective than aspirin and APAP, and may be equal to or greater than APAP/opioid combination products or opioids administered via injection, at recommended doses.
• Strong opioid full agonists are recommended as the first line treatment for severe pain.
• Full opioid agonists generally have no ceiling effect and the dose may be increased as tolerated based on adverse effects.
• Patients who do not respond to one opioid may respond to another. The choice of opioid should be based on adequate analgesia being provided with minimal adverse effects.
• When frequent as-needed dosing with short–acting agents becomes inappropriate, use of long-acting agents is warranted.
• Combination regimens, including opioids, non-opioids, and adjuvant analgesics, are useful for severe chronic pain.</td></tr>
<tr><td>American College of Physicians (ACP):
Guidelines for the Diagnosis and Treatment of Low Back Pain (LBP) (2007)[46]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work), and duration of symptoms.
• The potential interventions for lower back pain are outlined below:
Interventions for the Management of LBP
<table><tr><th>Intervention type</th><th>Acute pain (duration < 4 weeks)</th><th>Subacute or chronic pain (duration > 4 weeks)</th></tr><tr><td>Self-care</td><td></td><td></td></tr><tr><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr><tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr><tr><td>Books, handouts</td><td>Yes</td><td>Yes</td></tr></table></td></tr>
</table>

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Clinical Guideline	Recommendations

APAP	Yes	Yes
Tricyclic antidepressants	No	Yes
Benzodiazepines	Yes	Yes
NSAIDs	**Yes**	**Yes**
Skeletal muscle relaxants	Yes	No
Tramadol, opioids	Yes	Yes
Nonpharmacologic therapy		
Acupuncture	No	Yes
Cognitive behavior therapy	No	Yes
Exercise therapy	No	Yes
Massage	No	Yes
Progressive relaxation	No	Yes
Spinal manipulation	Yes	Yes
Yoga	No	Yes
Intensive interdisciplinary rehabilitation	No	Yes

Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

- Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
- In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, APAP or NSAIDs are the first-line options.
- APAP is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
- Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with APAP or NSAIDs. Evidence is insufficient to recommend one opioid over another.

A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: **Diagnosis and Treatment of**	• Clinicians should consider the use of medications with proven benefits in conjunction with self-care. • Clinicians should assess the severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy.

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Clinical Guideline	Recommendations
LBP (2007)[47]	• For most patients, first-line medical options are APAP or NSAIDs. • Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution. • Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
The Family Practice Pain Education Project: **Management of Pelvic Pain from Dysmenorrhea or Endometriosis (2004)**[48]	Dysmenorrhea • NSAIDs and COX-2-specific inhibitors should be used as initial treatment and started 1 to 2 days before menses and continued for 2 days after menses starts. • Contraceptive pills or medroxyprogesterone can be added to achieve control if NSAID/COX-2 treatment alone is not adequate. • Topical heat at 38.9°C used for 12 hours per day has been found to be as beneficial as ibuprofen. • Transcutaneous electrical nerve stimulation (TENS), acupuncture, daily thiamine, omega-3 fatty acids and nitroglycerin patches have limited evidence of efficacy. These alternative treatments can be used alone or as adjuvants to standard therapy. • After endometriosis has been ruled out by laparoscopy, invasive treatment options including uterosacral nerve ablation, presacral neurectomy or nerve block procedures can be considered. Endometriosis • NSAIDs, COX-2 inhibitors, oral contraceptive pills, gonadotropin-releasing hormone (GNRH) agonists, progestins, or danazol are treatment options. • NSAIDs or COX-2 inhibitors are used initially at maximal or nearly maximal dosage. There is no evidence to support switching from one NSAID to another to improve response, although the practice is frequent. • Oral contraceptive pills are used if pain relief has not been achieved with NSAID therapy and may be used alone or in combination with NSAIDs. • Using 3 months of contraceptive pills before a week without pills can reduce the number of menses, thus improving the quality of life. There is no evidence to support switching from one oral contraceptive pill to another to improve response.
Society of Obstetricians and Gynecologists of Canada: **Primary Dysmenorrhea Consensus Guideline (2005)**[49]	Nonpharmacological Treatment • Unlike low-frequency TENS, high-frequency TENS provides more effective dysmenorrhea pain relief compared with placebo and may be considered as a supplementary treatment in women unable to tolerate medication. • There is limited evidence that acupuncture and topical heat therapy may be of benefit in the management of primary dysmenorrhea. • There is no evidence to support spinal manipulation as an effective treatment option.

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Clinical Guideline	Recommendations

	Pharmacological Treatment
	• NSAIDs are considered a first-line treatment for the relief of pain and improvement in daily functioning unless there is a contraindication to therapy.
	• Oral contraceptives may be recommended for the treatment of primary dysmenorrhea. The added contraceptive effect may make oral contraceptives a first-line therapy for some women. In addition, consideration may be given to continuous use of oral contraceptive pills for withdrawal bleeding and the associated dysmenorrhea.
	• Depot medroxyprogesterone acetate and levonorgestrel intrauterine system can be considered treatment options in the management of primary dysmenorrhea.
	• Vitamin B1 has limited evidence regarding its efficacy and may be considered in the treatment of primary dysmenorrhea.
	• The following complementary and alternative medicines have shown an initial positive response for the treatment of primary dysmenorrhea and merit further study:
	  ○ Vitamin E
	  ○ Fish oil / Vitamin B12 combination
	  ○ Magnesium
	  ○ Vitamin B6
	  ○ Toki-shakuyaku-san
	  ○ Fish oil
	  ○ Neptune krill oil
	• Vitamin B6 in combination with magnesium, vitamin E in addition to ibuprofen and fennel have not been shown to have any benefit in the treatment of primary dysmenorrhea.

American College of Rheumatology Subcommittee on Rheumatoid Arthritis: **Guidelines for the Management of Rheumatoid Arthritis (2002)**[50]	• NSAIDs should be used as initial therapy to reduce pain and swelling, and to improve joint function.
	• Since they do not alter the course of the disease (i.e. preventing joint destruction), NSAIDs should not be used as monotherapy.
	• Therapy with disease modifying anti-rheumatic drugs (DMARDs) should begin within 3 months of an established diagnosis of rheumatoid arthritis in any patient who continues to experience any of the following symptoms despite an adequate trial of an NSAID therapy:
	  ○ Ongoing joint pain
	  ○ Significant morning stiffness or fatigue
	  ○ Active synovitis
	  ○ Persistent elevation of ESR or CRP
	  ○ Radiographic joint change
	
	DMARD Therapy
	• Therapy includes: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, etanercept, infliximab, azathioprine, D-penicillamine, gold salts, minocycline, cyclosporine.
	• Agent selection depends on individual patient characteristics, severity of the disease/disease progression and available data.
	• Changing and/or adding DMARDs should be considered if monotherapy is not sufficient.

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Clinical Guideline	Recommendations
	Anti-TNFα Therapy • Therapy includes: etanercept (Enbrel®) and infliximab (Remicade®). • Due to alterations in immune system function, agents must be used with caution in patients with susceptibility to infection or a history of tuberculosis; and should be avoided in patients with significant chronic infections. Discontinue temporarily in all patients with an acute infection. • Other agents have become available and approved for rheumatoid arthritis since this guideline update.
British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)**[51]	Management of Acute Gout • After an acute gout episode, affected joints should be rested and analgesic and anti-inflammatory drug therapy should be commenced immediately and continued for 1 to 2 weeks. • Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications. • Physicians should follow standard guidelines for the use of NSAIDs and COX-2 inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations. • Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy. • Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally. • Opiate analgesics can be used as adjunct therapy. • Intra-articular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments. Diet, Lifestyle Modification and Non-pharmacological Therapy • In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack. • Affected joints should be elevated and exposed in a cool environment. • Moderate physical exercise should be encouraged. Management of Recurrent, Intercritical and Chronic Gout • The plasma urate should be maintained below 300 µmol/L. • Uric acid lowering drug therapy should be started if further attacks occur within 1 year and should also be offered to patients with tophi, renal insufficiency, uric acid stones and to patients who need to continue treatment with diuretics. • Uric acid-lowering drug therapy should be delayed until 1 to 2 weeks after inflammation has settled. • Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increasing by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma urate <300 µmol/L) or maximum dose (900 mg daily) is

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Clinical Guideline	Recommendations
	reached. • Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulphinpyrazone in patients with normal renal function or benzbromarone in patients with mild to moderate renal insufficiency. • Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to 6 months. An NSAID or COX-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the duration of therapy should be limited to 6 weeks. • Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided.

Conclusions

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is more selective for cyclooxygenase-2 (COX-2) and has demonstrated lower rates of gastrointestinal adverse effects as well as an absence of effects on platelet aggregation. The manufacturer of celecoxib was asked by the Food and Drug Administration (FDA) to revise the product labeling and include a boxed warning, highlighting the potential for an increased risk of cardiovascular events and potential life-threatening gastrointestinal bleeding associated with their use. Celecoxib is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery.[9] Clinically, study results have shown celecoxib to be no more efficacious than traditional NSAIDs in treating the signs and symptoms of rheumatoid arthritis and osteoarthritis.

There is concern over the long-term safety of celecoxib on gastrointestinal as well as cardiovascular events. The results of the VIGOR[52] study found an association between rofecoxib and an increased rate of cardiovascular events. However, most observational studies performed since have leaned toward a cardioprotective effect of naproxen as the explanation for the increase in events, not a prothrombotic effect of rofecoxib.

Formal pharmacoeconomic analyses involving COX-2 inhibitors have been performed in other countries, namely Switzerland[53] Canada[54] and Sweden.[55] All of these analyses have found COX-2 inhibitors to be cost-effective, particularly in Europe, where their direct cost is not significantly different from that of conventional NSAIDs.

The use of celecoxib should be limited at this time to patients who are at high risk of gastrointestinal side effects (e.g., those having a history of gastrointestinal bleeding; those receiving chronic; high-dose systemic corticosteroids) or to patients who cannot tolerate traditional NSAIDs.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Celebrex® requires prior authorization for patients who are younger than 60 years of age with the following approval criteria:

- The patient does not have a history of a sulfonamide allergy.

AND

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- The patient has had a documented side effect, allergy, or treatment failure to two or more preferred generic NSAIDS.

OR

- The patient has a contraindication to medications not requiring prior approval, including:
  - History of GI bleed
  - Patient is currently taking an anticoagulant (warfarin or heparin)
  - Patient is currently taking an oral corticosteroid
  - Patient is currently taking methotrexate

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